REMARKS

Status of Claims

Claims 1-114 were originally pending in the present application. Claims 42-114 were withdrawn from consideration and claims 8, 11-17, 59, 61-67, 87, and 114 were cancelled. By virtue of this amendment, claims 1 and 27 have been amended and new claims 115-116 have been added.

Support for the amendment of claims 1 and 27 and the addition of new claims 115-116 can be found throughout the specification and claims, as originally filed, and, in particular on page 14, lines 20-21 and in the Examples on page 27, lines 6-14.

With respect to claim amendments and cancellation, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Request for Examiner Interview

Should the Examiner not consider the amendments and arguments put forth herein wholly persuasive, the Applicants hereby request the opportunity of an Examiner Interview prior to the issuance of a further Office Action on the present application. The Examiner is respectfully requested to contact the undersigned prior to the issuance of the next action in order to schedule the Examiner Interview.

Regarding the Supplemental Information Disclosure Statement

The Applicants thank the Examiner for his review of the references submitted with the Supplemental Information Disclosure Statement filed November 15, 2005 and for the return of the

initialed PTO SB/08.

Clarification of the Record

On page 5, 1st ¶, of the Office Action mailed December 22, 2005, the Examiner states that the material Pavelka used (65 mg/ml collagen with 0.3% lidocaine):

> ...overlaps with the claimed limitation of a collagen at a concentration of from about 3 mg to about 100 mg/ml and meet[s] the limitations of claims 19 and 25 which is at a concentration of about 65 mg/ml.

However, the Applicants note that claims 19 and 35 ultimately depend from claims 1 and 27, respectively, which each require that the collagen and pharmaceutical agent (anesthetic for claim 1 and bupivacaine for claim 27) are in a ratio of from about 0.5:1 to about 10:1 collagen: pharmaceutical agent. As the dependent claims must incorporate all of the limitations of the claims from which they depend, the material used by Pavelka does not teach the use of the composition claimed in claims 19 and 35, as the Pavelka material is in a ratio of collagen: pharmaceutical agent of approximately 22:1 and therefore does not meet the limitations of claim 1, from which claims 19 and 35 depend.

On page 5, 2nd ¶, of the Office Action mailed December 22, 2005 the Examiner states that:

> Further, Applicant continues by stating that the remaining secondary references cited, Yamahira et al., Maeda et al., and Batyrov et al. do not discuss the uses of collagen, but these secondary references neither teach nor suggest the use of the specific collagen as recited in the claims, nor do they suggest that preparations that are aqueous dispersions of the particular collagen recited in the claims.

The Applicants respectfully submit that in their response to the Office Action filed

November 15, 2005 they characterize the secondary references (Yamahira et al., Maeda et al., and Batyrov et al.) as discussing the uses of collagen, but consistently stated throughout the response that the secondary references did not teach nor suggest the use of aqueous dispersions of insoluble non-crosslinked fibrillar type I atelopeptide collagen. As noted in the above-referenced response, each of the references characterized the collagen used therein as being a "solution" when in aqueous solvent and therefore fully dissolved (*i.e.,* soluble collagen and not a dispersion), while the collagen described and claimed in the present application is *insoluble* and therefore must be a different type of collagen than the collagen described in the secondary references.

Rejections under 35 U.S.C. §103

Claims 1-7, 9, 10 and 18-41 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Pavelka et al., Poster No. 137 of "Safety Following Intra-articular Injection of Neu Visc™--Two Studies" taken with Yamahira (U.S. Pat. No. 4,855,134), Maeda et al., (J. Controlled Release, Vol. 62, pp. 313-324, Batyrov et al., (Stomatologiya, Vol. 61(2), pp.7-10, March-April, 1982, English Abstract) and Solanki et al., (Arthroscopy, Vol. 8(1), pp. 44-47, 1992). The Applicants respectfully traverse the rejection.

While the Applicants do not agree with the basic assertions put forth by the Examiner with respect to the rejections under 35 U.S.C. §103 and, in particular the applicability of the teachings of the secondary references (Yamahira et al., Maeda et al., and Batyrov et al.) with respect to compositions incorporating aqueous dispersions of *insoluble* non-crosslinked fibrillar type I atelopeptide collagen, in the interests of efficiently moving the prosecution of the present application forward, Applicants provide the comments appearing below and have amended claims 1 and 27, and therefore their dependent claims.

The Applicants submit that claims 1 and 27, as amended, and their dependent claims, are not obvious in view of the above-listed references. Specifically, the cited references do not teach nor suggest the compositions as claimed in claims 1-7, 9, 10 and 18-41, where the melting temperature of the composition is from about 42°C to about 46°C and the ratio of collagen:

pharmaceutical agent is from about 0.5:1 to about 10:1.

As noted in Example 1 (particularly page 27, 2nd ¶) of the present specification, when the insoluble non-crosslinked fibrillar type I atelopeptide collagen is prepared as an aqueous dispersion with anesthetic (bupivacaine) according to the ratio of collagen: pharmaceutical agent as presently recited in the claims, the composition exhibited a prominent new peak in the DSC thermogram, melting at about 45°C and, concomitantly, showed a delayed release of the anesthetic (*see e.g.,* Figs. 1-3). As noted in the specification, this data is indicative of a structural change in the collagen that appears correlated with the controlled release characteristics of the composition. There is no suggestion or teaching in Pavelka that the ratio of collagen: pharmaceutical agent used in Pavelka would result in a composition having this melting temperature.

With respect to the secondary references of Yamahira et al., Maeda et al., and Batyrov et al., as noted previously, these references appear to use an entirely different type of collagen than that presently claimed and described, namely a *soluble* form of collagen (and Solanki et al., makes no mention at all of collagen). As is well known to those of skill in the field, the different forms of collagen (*e.g.,* fibrillar vs. non-fibrillar, soluble vs. insoluble, etc.) have different structural characteristics and, because of these different structural characteristics have different effects on the release of pharmaceutical agents. Therefore, it is unlikely that the soluble forms of collagen taught in the secondary references could have the same melting temperature (DSC thermogram) as the presently claimed compositions. And, as noted above, there is no teaching nor suggestion of melting temperatures in the secondary references.

Additionally, contrary to the Examiner's assertions, the skilled practitioner would not be motivated to combine the features of the secondary references (*e.g.,* collagen concentration, collagen: pharmaceutical agent ratio, etc.) to modify the collagen formulation used in Pavelka, because it was well known that in addition to structural differences, the different forms of collagen have very different pharmacokinetic profiles with respect to drug release. Prior to the filing of the present application, it was not known that collagen compositions where the collagen component consisted essentially of insoluble non-crosslinked fibrillar type I atelopeptide collagen (as presently

claimed) could be used to achieve controlled release of small molecules such as bupivacaine/anesthetics (*see* Response to Office Action dated 11/15/05, pp. 19-20 and Wallace *et al., Advanced Drug Delivery Reviews* (2003) **55**: 1631-1649). None of the secondary references teach or suggest the suitability of the use of aqueous dispersions of *insoluble* non-crosslinked fibrillar type I atelopeptide collagen in the formulations described in the secondary references (which all utilize *soluble* forms of collagen) and, based on the known structural differences and known pharmacokinetic differences between the various forms of collagen at the time of filing of the present specification, the skilled artisan would not be motivated to combine the features described in the secondary references with regard to *soluble* collagen to modify the dispersions used in Pavelka.

As noted previously (Response to Office Action filed 3/17/05, pp. 22-23), the concentration of lidocaine (anesthetic) present in the Pavelka formulation would not be effective to achieve an anesthetic effect for more than an hour or so at most, and likely far less. The pain relief 6 weeks after injection afforded by the formulation used by Pavelka and referred to by the Examiner (Office Action mailed 12/22/05, bridging paragraph pp. 4-5) cannot therefore be due to an anesthetic effect, as would be recognized by the skilled practitioner, who would, as explicitly suggested by Pavelka et al. ((June 1999) "Pain Reduction in Knee Osteoarthritis: A Novel Treatment Using Intra-articular Type I Collagen NeuVisc™ Synovial Fluid Supplement," Presented at 4th Congress of the European Federation of National Associations of Orthapaedics and Traumatology, Brussels, Belgium) attribute the reduction of pain to the formulation's action as a synovial fluid supplement (page 1, column 1, 1st & 2nd bullet points). Action as a synovial fluid supplement/viscosupplement is consistent with the results that patient pain continues to decrease through the 6 week time point assessed by Pavelka, a period of time at which any anesthetic effect would have dissipated. In other words, to a skilled practitioner, the formulation of Pavelka would be viewed as a viscosupplement/synovial fluid supplement that is a dispersion of insoluble collagen while the formulations of Yamahira et al., Maeda et al., and Batyrov et al., are drug delivery formulations prepared from solutions of *soluble* collagen, and it there would be no motivation to combine the two different types of formulations to achieve a drug delivery formulations

incorporating a dispersion of insoluble collagen with the ratio of collagen: pharmaceutical agent and melting temperature as presently claimed.

In view of the above remarks and amendments the Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is earnestly entreated to telephone the undersigned at the number given below prior to the issuance of a further action in the present application.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **437252001200**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 20, 2006

Respectfully submitted,

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